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Original Research Article

Suzetrigine: A First-in-class $Na_V1.8$ Inhibitor for Opioid-free Pain Management

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Bala Ashwathy Radhakrishnan Malarvizhi[1], Indumathi Prabath[2], Sangeetha Raja[1] and Jamuna Rani[1]

Abstract

Background: Opioids have been an integral part of pain management for many years. With the increasing global burden of opioid dependence, the development of non-opioid therapies provides a new framework for pain management. Suzetrigine is a stepping stone toward non-opioid treatment methods.

Objectives: To summarize the pharmacological profile, preclinical and clinical trial evidence of suzetrigine in opioid-free pain management.

Materials and Methods: Published research, clinical trial data, and review articles from PubMed, Cochrane, and Google Scholar were reviewed from January to July 2025. The findings have been consolidated in this article to summarize them in relation to suzetrigine to provide an overview from pharmacological and clinical perspectives.

Results: *In vitro* and *in vivo* studies demonstrated the voltage-gated sodium channel, $Na_V1.8$, selective property of the drug. Vertex Pharmaceuticals has conducted four randomized controlled trials (two Phase 2 and two Phase 3 [NAVIGATE-1 and NAVIGATE-2]) and one open-label trial to assess the efficacy and safety profile of suzetrigine. Significant pain reduction was observed with suzetrigine compared to that with placebo. Nausea was the most common adverse effect observed with the drug; however, the drug was otherwise well tolerated and showed low abuse potential. The United States Food and Drug Administration approved suzetrigine for the treatment of moderate to severe acute pain on January 30, 2025. Several trials for the application of the drug in the management of chronic pain are ongoing, among which some have reported promising results. This review summarizes the pharmacological profile of suzetrigine, its future perspectives, current trends, and potential changes in pain management.

Conclusion: Suzetrigine is a first-in-class non-opioid analgesic and $Na_V1.8$ inhibitor, approved only for the treatment of moderate to severe acute pain. With a less addictive nature and good safety profile, its potential in the management of conditions with chronic pain is yet to be elucidated from clinical trials with a long-term follow-up period.

Keywords

Analgesia, $Na_V1.8$ channel, non-opioid, pain, suzetrigine

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Introduction

Pain is a universal complaint across all age groups.[1–3] Its mechanism is influenced by diverse cultural and historical perspectives.[2,3] Being subjective, pain is difficult to quantify. The International Association for the Study of Pain (IASP), established in 1973, advanced the understanding of pain mechanisms.[2] The IASP, in 1979, defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[4,5] With growing scientific knowledge, ICD-11

[1]Department of Pharmacology, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Chengalpattu, Tamil Nadu, India
[2]Department of Pharmacology, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, Tamil Nadu, India

Corresponding author:
Bala Ashwathy Radhakrishnan Malarvizhi, Department of Pharmacology, First Floor, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu 603203, India.
E-mail: birlabala@gmail.com

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introduced a new pain classification (2013), later adopted by the WHO in 2019.[5] In 2020, viewing pain as a global healthcare issue, the IASP revised the definition as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[5–7] Several theories explain the pain neuromatrix, including nociceptive component and its translation to Gate Control Theory, Bayesian Model, High-order, Global-workspace, and Information Theory.[4] Pain occurs when internal or external stimuli are transduced into nerve impulses via nociceptors and mechanoreceptors supported by ion channels.[4,8] Although the initial focus was on the central nervous system (CNS), the role of the peripheral nervous system in initiating and modulating pain is now being recognized.[4] Opioids remain a mainstay, but discovering voltage-gated sodium channel expression in the peripheral nervous system[9–12] led to the development of newer analgesics, among which $Na_V1.8$ expression and inhibition are clinically significant.

WHO Guidelines

Classifying pain as acute or chronic helps to identify the etiology.[3] Evidence of endogenous neurochemical reactions, opiate receptors, and psychological factors supports customized pain management.[3,7] Following international expert discussions, WHO introduced the three-step analgesic ladder, a guideline for cancer-related pain relief in 1986 for adults[13,14] and in 1998 for children.[13] The first step addresses mild pain, and moderate and severe persistent pain subsequently.[14] In 1996, a fourth step was added for acute pain.[14] Downward and upward approaches were formulated for acute and chronic pain, respectively, with analgesic platform or trolley methods incorporating non-pharmacological strategies.[15–18] A "reverse pain ladder" for discharge planning after treatment for acute pain has also been proposed.[19]

Trends in Pain Management and New Analgesics

A multimodal strategy is essential for all age groups and pain types.[13,17,20–22] Targeting different levels of the pain pathway enables a non-opioid approach, especially in the peripheral nervous system.[8,23] Voltage-gated sodium channel blockers emerged from understanding nociception and ion channels in pain signaling.[9–11,24] Neurotoxins, such as tetrodotoxin (TTX), act on tetrodotoxin-sensitive (TTX-S) subtypes $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, $Na_V1.4$, $Na_V1.6$, and $Na_V1.7$.[10,25] TTX lacks affinity for myocardial $Na_V1.5$ at therapeutic doses.[25] Intramuscular and intravenous administration showed a narrow therapeutic index, while oral administration of local anesthetics and vasoconstrictors widened the therapeutic index.[25] Analgesic effects have been demonstrated on neuropathic, inflammatory, acute, chronic, visceral, and malignant pain models at sublethal doses.[25] Other neurotoxins, such as neosaxitoxin, produced minimal nerve conduction block.[10,26] Trials confirm potentiation of the local anesthetic effect of neosaxitoxin when coadministered subcutaneously with bupivacaine and epinephrine.[26] Batrachotoxin, peptide-based venom, or toxins from scorpions, spider-like protoxin, huwentoxin, and pyrethroid also modulate Na_V function.[26] Lidocaine and fentanyl were repurposed for their analgesic effect. First-generation Na_V modulators were non-selective and caused state-dependent block, binding to the inner pore of the channel. This includes lidocaine, phenytoin, and anti-arrhythmic drugs. Due to systemic side effects from lack of selectivity, first-generation drugs are not preferred for chronic pain management.[10] The second-generation drugs include ralfinamide and lacosamide. Ralfinamide blocks N-type Ca^{2+} channels and *N*-methyl-d-aspartate (NMDA) receptors, other than state- and use-dependent Na_V block. Lacosamide enhances slow inactivation of Na_V, reducing hyperexcitability on repetitive neuronal signaling, unlike the first-generation drugs, which stabilize fast inactivation, blocking excess Na influx in a single action potential. For TTX-S Na_V selectivity, especially $Na_V1.7$, lacosamide was approved as an anti-convulsant and is used for diabetic neuropathic pain management. Later came the second- and third-generation sodium channel modulators with specific target sites, especially $Na_V1.3$, $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ expressed in sensory receptors. $Na_V1.7$, for its genetic implication in pain sensation, and $Na_V1.8$, being TTX-resistant, are the major pain relief targets.[10]

Current analgesics for chronic pain, such as opioids, dorsal root ganglionic stimulation (DRGS), peripheral nerve stimulation (PNS), and telemedicine, act on the CNS.[27] Drugs targeting $Na_V1.1$, $Na_V1.3$, and $Na_V1.7$ aim to overcome CNS-associated adverse effects like sedation, dependence, euphoria, and addiction.[8,24,25]

Selective $Na_V1.7$ inhibitors, such as PF-05089771 and CNV1014802, and $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ blockers, such as DSP-2230 (ANP-230), are currently under clinical trial.[10] $Na_V1.8$-specific drugs such as A-803467, VX-128, and VX-150 failed with serious adverse reactions in Phase 1 studies.[28] VX-548 performed better, and after two successful Phase 3 clinical trials, the Food and Drug Administration (FDA)-approved VX-548 as suzetrigine for acute pain management on January 30, 2025. Other $Na_V1.8$ inhibitors are in Phase 1 and Phase 2 clinical trials.[29] Suzetrigine is challenged by cost and limited efficacy compared to gene therapy targeting $Na_V1.7$ and $Na_V1.8$.[30]

Opioid Epidemic

Therapeutic and illicit opioid misuse remains a major concern.[7,26] Long-term use resulted in relapse and remission of opioid use disorder (OUD).[26,31] From 1989 to 2009, opioid use peaked globally.[19] An observational epidemiological study conducted based on the 2019 Global Burden of Disease Study showed an escalation in the incidence, prevalence, and mortality of OUD among adolescents and young adults from 1990 to 2019.[32] In 2019, globally, 43,447

adolescents and young adults died from OUD.[32] Men predominated in high sociodemographic index countries.[32] However, after 2014, the incidence in females increased. The World Drug Report from the Centers for Disease Control and Prevention (CDC) reported a 38% increase in mortality from opioid overdose, with 70% of drug-overdose deaths due to opioids.[33] Although opioid dependence can be treated with naloxone, naltrexone, methadone, and buprenorphine, measures to prevent opioid addiction are important.[19,26] Psychosocial factors influence relapse or opioid dependence recurrence.[34] Both genetic and environmental factors predispose opioid addiction.[35] Neurocircuit dysregulation involving reward-stress function contributes to OUD.[35] Genomic biomarkers are being explored to enable personalized risk prediction in chronic opioid users.[33,35] A recent study integrated genome-wide association study (GWAS) traits with *in silico* analytic methods, such as protein–protein interaction (PPI) and enrichment analysis (EA), identified 50 genes linked to pain, opioid use, and inflammation, highlighting μ-opioid receptor (OPRM1), dopamine receptor (DRD2), glutamate receptor (GRIN2B), GPR98, and APOE with implications for neurological disorders and lipid metabolism.[36] It proposed a combination of high-density lipoprotein (HDL)-boosting drugs and dopamine-boosting regulators, such as KB220, to reduce relapse.[36] Therefore, opioid addiction can be predicted prior to usage. Another study used next-generation sequencing (NGS) to identify genetic variants (single-nucleotide variants) predisposing OUD, using RNA-sequencing data from postmortem ventral midbrain tissue of chronic opioid users. Out of eight genes, NRXN3 (Neurexin 3), involved in synaptic transmission, had the highest number of variants in chronic opioid users.[33] Thus, non-opioid analgesics are promising alternatives for acute pain.

Methodology

Published research and review articles related to pain were searched from PubMed, Cochrane, and Google Scholar. In addition, clinical trial data from NCT04977336, NCT05034952, NCT05660538, NCT06176196, NCT05553366, NCT05558410, and NCT05661734 were reviewed. Keywords used for the search were pain, suzetrigine, Na_V, opioids, and analgesia. Only articles published from January to July 2025 were included in this review article. Both preclinical and clinical studies were included. The results were consolidated for a pharmacological and clinical overview of suzetrigine.

Results

This section summarizes preclinical and clinical trial data of suzetrigine. This includes pharmacokinetics, efficacy, and safety outcomes from the studies.

Preclinical Study (In Vitro and In Vivo)

Preclinical *in vitro and in vivo* studies demonstrated high selectivity of suzetrigine.[37] Its specific binding site is on the voltage-sensing domain 2 (VSD2) in the closed state of the channel, confirmed by introducing $Na_V1.8$'s VSD2 into $Na_V1.2$ using a domain-swapping strategy.[37] $Na_V1.2$, unresponsive or insensitive to suzetrigine, showed sensitivity to the drug when attached to VSD2 and no other voltage-sensing domains (VSD1, VSD3, and VSD4) of $Na_V1.8$. Thus, VSD2 plays a key role in the drug sensitivity of $Na_V1.8$.[6,20,37] Direct binding to VSD2 was confirmed by using radiolabeled suzetrigine. Some studies suggested that the binding site is based on the extracellular loop of S3–S4 segments of VSD2, while others point out the KKGS sequence—a unique amino acid motif in the S3–S4 extracellular loop in $Na_V1.8$—to confer sensitivity in $Na_V1.8$ to suzetrigine through experiments.[37,38] VSD2 regulates pore opening. Unlike anesthetics that bind to the inner pore of the channel or open state, suzetrigine interferes with the movement of VSD2 in its resting state or conformation to modify the gating mechanism externally. Eventually, $Na_V1.8$ is stabilized in the closed or resting state, inhibiting further activation or opening to nerve signals. This causes allosteric and tonic state-dependent inhibition rather than a simple channel-blocking mechanism.[31,37] To find out Na_V subtype selectivity and potency of suzetrigine, electrophysiological studies were performed using cell lines with stable or transient overexpression of Na_V channels such as Chinese hamster ovary (CHO), Human embryonic kidney (HEK), and ND7/23 (rodent neuroblastoma fusion).[37] The number of action potentials observed before and after the administration of suzetrigine, using the manual patch voltage clamp method, was used to assess the inhibition of suzetrigine effects.[37] No cardiovascular and respiratory adverse effects were observed in a single-dose Latin square design study conducted in monkeys. *In vivo* studies in rats and monkeys and clinical trials for CNS effects, adverse effects, and abuse potential favored a lower chance of addiction, despite crossing the blood–brain barrier, due to lack of $Na_V1.8$ expression in the CNS.[37] No behavioral changes or physical dependence were observed. However, the long-term safety profile and intensity of inhibition in correlation with efficacy have yet to be established through further clinical studies. Preclinical studies on its effects during pregnancy showed the findings presented in Table 1. In a rat study, preimplantation loss was attributed to the high sensitivity of rat progesterone receptors, unlike those in humans.[39] In addition, the effect on fertility was reversible. Stopping the drug 4 weeks prior showed no preimplantation loss. Preimplantation loss was observed only when the drug was administered before mating or until gestational day 7. To assess the systemic toxicity of suzetrigine and M6-SUZ, a repeat-dose study was done in rats and monkeys for 91 days and 28 days.[39]*In vitro Ames, in vitro*, and *in vivo* micronucleus assays were negative for mutagenicity and carcinogenicity of suzetrigine.[39]

Table 1. Summary of Preclinical Study of Suzetrigine in Pregnant Animal Models.[39]

Animal Model	Intervention			Observation
	Dose	Route	Time	
Pregnant rabbit	50 mg/kg/day 100 mg/kg/day 200 mg/kg/day	Oral	Organogenesis period	Up to 100 mg/kg/day, no adverse embryofetal events At 200 mg/kg/day: Increased post-implantation loss Low fetal body weight Maternal toxicity
Pregnant rats	5 mg/kg/day 10 mg/kg/day 15 mg/kg/day	Oral	Organogenesis period	Up to 10 mg/kg/day, no adverse embryofetal events At 15 mg/kg/day: Increased post-implantation loss Number of live fetuses reduced Low fetal body weight Placental transfer observed Mean gestational length reduced Postnatal mortality (up to day 4) increased

Pharmacokinetics of Suzetrigine

In vitro electrophysiological assays used manual patch voltage clamp experiments in isolated human and monkey dorsal root ganglia neurons to determine the IC_{50} as a measure of drug potency.[37] IC_{50} was 0.68 nM in humans, 0.75 nM in monkeys, and 56 nM in rodents, reflecting markedly lower rodent $Na_V1.8$ sensitivity. This 80-fold difference explains why rodent *in vivo* models were not used. *In vitro* human tissue studies demonstrated that M6-SUZ, the active metabolite, also blocks $Na_V1.8$. CYP3A enzymes form M6-SUZ.[40] Rat liver microsomes: M1 (O-desmethyl) and M2 (N-oxide), with M1 predominating in males, demonstrated sex-dependent metabolism in rats, unlike in humans.[37,40] This interspecies and sex-dependent metabolic variation influences the pharmacokinetics of the drug, limiting the translation of preclinical data to humans. The pharmacokinetic studies in rats, monkeys, and humans used liquid chromatography–mass spectrometry (LC–MS) bioanalytical assay to quantify the plasma concentrations.[1] The C_{max} was 0.62 µg/mL, and T_{max} was 3 h during the fasting state and 5 h during the fed state.[37,39] This explains the delayed onset of action in the fed state in Figure 1. Suzetrigine shows 99% plasma protein binding, a volume of distribution (Vd) of 495 L, and a half-life ($t½$) of ~23.6 h, reducing its clearance to ~3.9 L/h.[20,37,39] Suzetrigine is eliminated by oxidative metabolism, with 49.9% excreted in feces (M6-SUZ and suzetrigine) and 44% in urine (only M6-SUZ).[39] Bioavailability remains unreported.[39]Table 2 compares the pharmacokinetic parameters of suzetrigine and M6-SUZ.

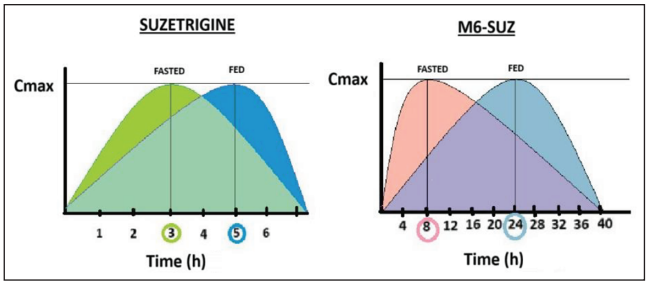


Figure 1. Effect of Food on Suzetrigine and M6-SUZ After Loading Dose.[1,39] In the Fed State, Time to Achieve Maximum Plasma Concentration (C_{max}) of Suzetrigine and M6-SUZ is Prolonged After the Loading Dose, Unlike the Fasting State. In the Fed State, C_{max} and Area Under the Curve (AUC) are Unaffected, but Time to Achieve Maximum Plasma Concentration (T_{max}) is Prolonged. Thus, Food Delays the Onset of Action of Suzetrigine.

Source: Created by the corresponding author using Paint software.

Table 2. Comparison of Pharmacokinetics of Suzetrigine and Its Active Metabolite[1,39]

Pharmacokinetic Parameters	Suzetrigine	M6-SUZ
Steady state C_{max} (µg/mL)	0.62	1.5
T_{max} (h)	3	10
Volume of distribution (L)	495	NA
Half-life ($t½$) (h)	23.6	33.0
AUC (µg-h/mL)	11.5 (25.6%)	34.7 (25.6%)

Note: AUC: Area under curve; C_{max}: Maximum plasma concentration; T_{max}: Time to reach maximum plasma concentration.

Clinical Trials

Five clinical trials—two Phase 2 and three Phase 3 (NAVIGATE-1, NAVIGATE-2, and single-arm study) trials—evaluated the efficacy and safety of suzetrigine.[41–43] The results are summarized in Table 3. Except for the Phase 3 single-arm study, all trials were randomized, double-blind, active- and placebo-controlled studies.[41,42] Abdominoplasty and bunionectomy served as soft- and hard-tissue pain models. The endpoints of NAVIGATE-1 and NAVIGATE-2 were the same, reporting efficacy using the sum of the pain intensity difference over 48 h (SPID48) as the primary endpoint and safety as the secondary endpoint.[41] The SPID48 was expressed as the least square (LS) mean difference. The results are presented in Figure 2. Higher SPID48 values indicate better pain relief. The open-label study included surgical

Table 3. Summary of Clinical Trials Conducted With Suzetrigine.

Trial Phase	Study Title, Authors, Year of Publication and ID		Intervention and Sample Size	Findings
Phase 2	Selective inhibition of $Na_V1.8$ with VX-548 for acute pain[8]	Bunionectomy (NCT04977336) Study ID: VX21-548-101	Suzetrigine 100 mg followed by 50 mg PO Q12H for 48 h versus placebo and acetaminophen/hydrocodone *n* = 274	Both are randomized, double-blind, placebo-controlled clinical trials Primary endpoint: SPID48 showed statistically significant pain reduction with suzetrigine at a higher dose (vs. placebo) The least square (LS) mean difference in SPID48 was 36.8 and 37.8 in bunionectomy and abdominoplasty, respectively Secondary endpoint: SPID24 showed 19.6 in abdominoplasty and 13.7 in bunionectomy study Safety: The most common adverse effects were mild to moderate headache and constipation
		Abdominoplasty (NCT05034952) Study ID: VX21-548-102	Suzetrigine 100 mg followed by 50 mg PO Q12H for 48 h versus placebo and acetaminophen/hydrocodone *n* = 303	
	Evaluation of efficacy and safety of VX-548 for painful diabetic peripheral neuropathy (DPN)[45]	Patients with painful diabetic peripheral neuropathy (NCT05660538) Study ID: VX21-548-103	Pregabalin versus placebo matched to suzetrigine Active comparator: Pregabalin 100 mg TDS × 12 weeks Experimental: Suzetrigine (SUZ) in low dose (23 mg OD × 12 weeks), mid dose (46 mg OD × 12 weeks), and high dose (69 mg OD × 12 weeks) versus placebo matched to pregabalin *n* = 194	Randomized, double-blind, active-controlled, dose-ranging, parallel-group study design Primary endpoint: Change from baseline in the weekly mean of the daily numeric pain rating scale (NPRS) score assessing average pain intensity in the last 24 h Secondary endpoints: Change from baseline in the weekly average of the daily sleep interference scale (DSIS) score, percentage of participants with greater than or equal to (≥) 30 % reduction from baseline in the weekly average of daily pain intensity on the NPRS, safety, and tolerability Incidence of serious adverse events was relatively higher in mid dose of suzetrigine than its high dose and pregabalin study group
	Evaluation of efficacy and safety of VX-548 for painful lumbosacral radiculopathy (PLSR)[46]	Patients with painful lumbosacral radiculopathy (NCT06176196) Study ID: VX23-548-109	VX-548 versus placebo for 12 weeks *n* = 218	Randomized, double-blind, placebo-controlled, parallel-group study design Primary endpoint: Change from baseline in the weekly average of daily leg pain intensity on a numeric pain rating scale (NPRS) until week 12 Secondary endpoint: Change from baseline in the weekly average of the daily sleep interference scale (DSIS) till week 12 and safety and tolerability with adverse events and serious adverse events till week 14 Statistically significant reduction in NPRS by 2.02 within the suzetrigine study group but the placebo-arm also showed similar results
Phase 3	Suzetrigine, a non-opioid $Na_V1.8$ inhibitor for treatment of moderate-to-severe acute pain: Two Phase 3 randomized clinical trials[41,43]	NAVIGATE - 1 (bunionectomy) NCT05553366 Study ID: VX22-548-104	Suzetrigine 100 mg followed by 50 mg PO Q12H for 48 h vs placebo and acetaminophen/hydrocodone *n* = 1,073	Primary endpoint: SPID48 (suzetrigine vs. placebo) Secondary endpoint: SPID48 (suzetrigine vs. acetaminophen/hydrocodone bitartrate) Suzetrigine showed statistically significant results in pain reduction compared to placebo in both trials Acetaminophen had better pain reduction compared to suzetrigine in NAVIGATE-1 but no statistical significance in both trials Exploratory analysis (suzetrigine vs. placebo) reported SPID24 using the LS mean
		NAVIGATE-2 (abdominoplasty) (NCT05558410) Study ID: VX22-548-105	Suzetrigine 100 mg followed by 50 mg PO Q12H for 48 h versus placebo and acetaminophen/hydrocodone *n* = 1,118	
	Suzetrigine, a non-opioid $Na_V1.8$ inhibitor with broad applicability for moderate-to-severe acute pain: A Phase 3 single-arm study for surgical or non-surgical acute pain[42]	Surgical and non-surgical acute pain (NCT05661734) Study ID: VX22-548-107	Suzetrigine 100 mg followed by 50 mg PO Q12H × 14 days *n* = 256	Single-arm study Included surgical (87%) and non-surgical (13%) moderate-to-severe acute pain Primary endpoint: Safety and tolerability Secondary endpoint: Effectiveness in acute pain using five-point Likert scale (83.2% reported as good/excellent effect) It has demonstrated good tolerability and potential as a monotherapy and in combination therapy with adverse events such as headache

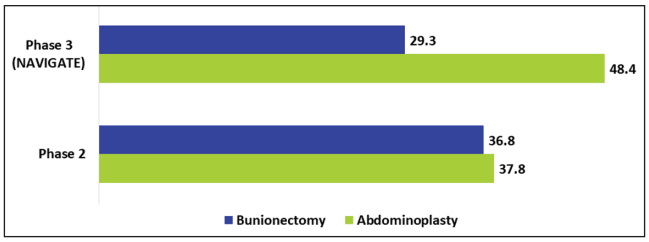


Figure 2. Least Square (LS) Mean Difference in SPID48 (Suzetrigine vs. Placebo).[1,39] The More the Difference in LS Mean, the Better the Pain Reduction. Suzetrigine Showed Better Pain Relief in Abdominoplasty in Both Phase 2 and 3 Studies.

pain from orthopedic procedures, most commonly ligament repair, arthrodesis, followed by liposuction, mammoplasty, nasal septoplasty, turbinoplasty, inguinal hernia repair and non-surgical pain from arthralgia, limb pain, and strain. The safety profile was consistent with controlled trials.[39] Overall, suzetrigine demonstrated superior efficacy compared to placebo at high doses during the postoperative period.[44] In a phase 3 abdominoplasty trial, suzetrigine produced better pain relief compared to placebo—119 versus 480 min in abdominoplasty and 240 versus 480 min in bunionectomy.[39]

These studies demonstrated the superiority of suzetrigine over placebo, but only at high doses, limited to 48 h post-surgery and a maximum of 14 days. Limited evidence on the dosage of active comparator (acetaminophen-hydrocodone) questions the efficacy of suzetrigine in a real-world clinical setting for chronic pain.[44]

Promising results from initial studies have promoted clinical trials for more commonly addressed chronic pain conditions, such as diabetic peripheral neuropathy and lumbosacral radiculopathy.[45,46] In Phase 2 study of lumbosacral radiculopathy, suzetrigine did not outnumber the placebo. In Phase 2 study of diabetic peripheral neuropathy, high-dose suzetrigine and placebo showed a better safety profile than mid-dose suzetrigine. A Phase 3 study on diabetic peripheral neuropathy is currently ongoing. As suzetrigine failed to outnumber placebo in a Phase 2 trial with lumbosacral radiculopathy, approval for advancement to Phase 3 is pending. As suzetrigine has been approved only for the management of acute pain, its analgesic potential in chronic pain depends on the awaited outcomes of ongoing trials and further studies.

Safety Profile

The trials demonstrated suzetrigine to be a safe drug with no abuse potential in the population studied for a particular dosage.[39] The most common adverse effect of suzetrigine in Phase 3 trials (NAVIGATE-1 and NAVIGATE-2) was nausea or vomiting (20% in abdominoplasty and 9% in bunionectomy patients). The other adverse effects included pruritus (18%), muscle spasm (11%), increased blood levels of creatine phosphokinase (CPK) (10%), and rash (10%).[39] Nearly 2.9% of participants in the suzetrigine group had CPK levels three times higher than the normal upper limit. Approximately 2.5% of participants treated with suzetrigine in the NAVIGATE-1 and NAVIGATE-2 trials had a reduction of ≥25% and <50% in estimated glomerular filtration rate (eGFR), respectively. A reduction in eGFR was also reported in the open-label Phase 3 trial; however, the values returned to baseline during follow-up. Although there was no adverse event due to this change, the reason was not stated; however, it is recommended to avoid the drug in patients with renal impairment or dysfunction. In addition, the incidence of adverse effects of suzetrigine was lower than that of hydrocodone bitartrate/acetaminophen and placebo. Adverse effects were more common in the acetaminophen treatment group than in the placebo group. Figure 3 shows the incidence of adverse effects in the three treatment arms. In addition, the safety profile of suzetrigine in the Phase 3 open-label trial was consistent with that in NAVIGATE-1 and NAVIGATE-2.

Preclinical toxicity studies have demonstrated the potential of suzetrigine to affect fertility, pregnancy, and fetal growth in pregnant animal models.[39] Despite the physiological differences between animal models and humans, the use of suzetrigine should be avoided. In NAVIGATE-1 and NAVIGATE-2, the change in mean systolic and diastolic blood pressure in the suzetrigine group compared with the placebo group was not clinically significant.[1,39] Most of the adverse events during the trial were mild and self-limiting. The incidence of serious adverse events and adverse events leading to discontinuation was minimal in this study. No specific antidote has been developed for drug overdose or drug toxicity. Supportive treatment with monitoring of clinical status and vitals is recommended.[39]

Discussion

The trial outcomes demonstrate the efficacy of suzetrigine in the management of moderate to severe acute pain of surgical and non-surgical etiology only. With good safety outcomes, its potential in chronic pain management is being studied in the ongoing trials. The FDA-approved therapeutic uses, dosage, route of administration, drug and food interactions, and application in special populations are discussed below.

Role of $Na_V1.8$ in Pain Signaling

Voltage-gated sodium channels regulate the cell membrane potential and vary by alpha subunit expression, coded by the SCN gene. They are expressed in the CNS, peripheral nervous system, or both. $Na_V1.8$ channels are mainly expressed in the dorsal root ganglion, nociceptors, and pain pathway signaling, but not in the CNS.[37,47,48] Initial studies found $Na_V1.8$ to be tetrodotoxin-resistant (TTX-R), with selective expression in dorsal root ganglion neurons of small-diameter like C-type nociceptive fibers.[28,49] Electrophysiological studies show a positive correlation between $Na_V1.8$ expression and both the duration and amplitude of action potential, suggesting that $Na_V1.8$ is involved in the nociceptor and

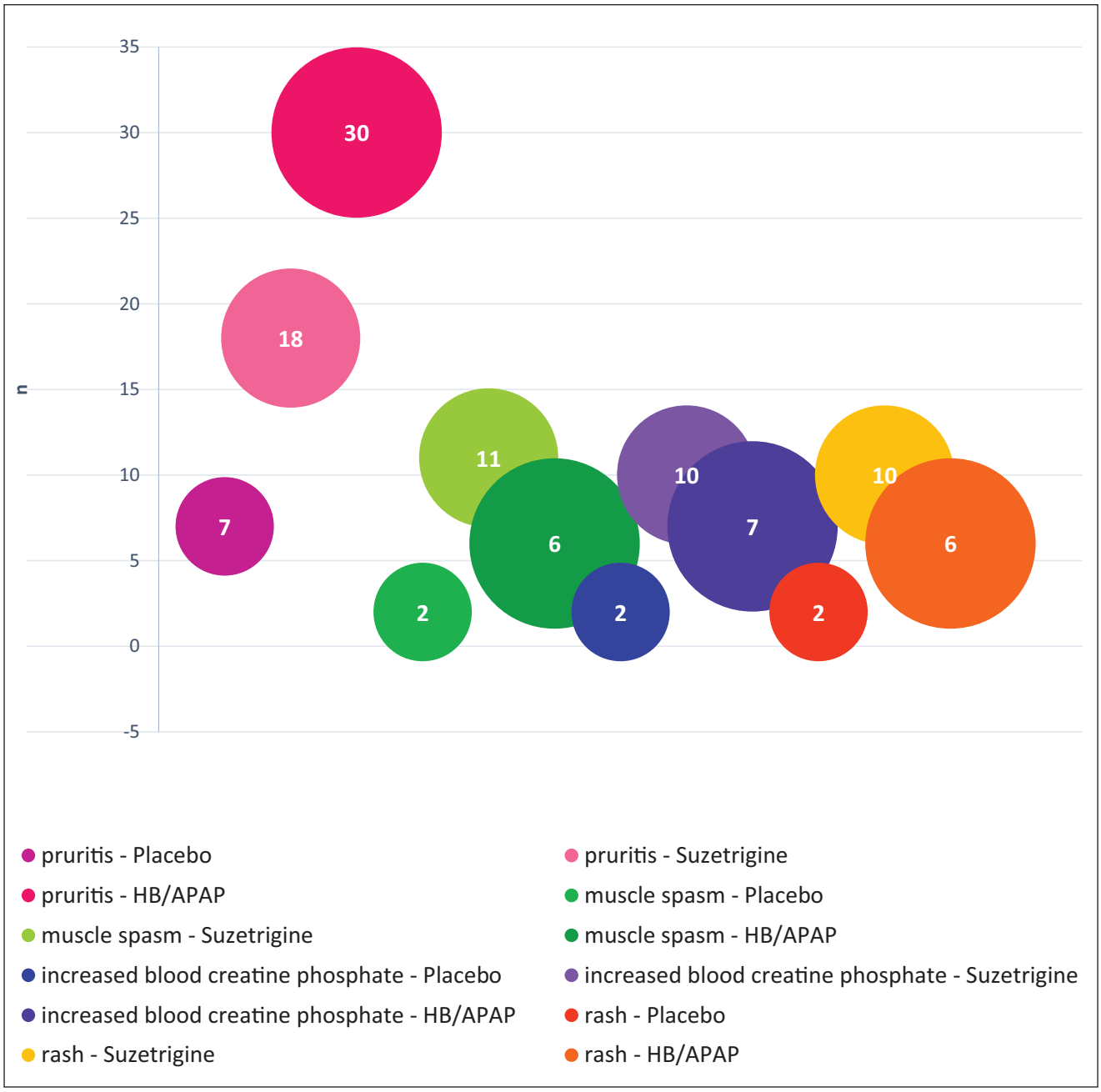


Figure 3. Adverse Reactions Reported in Two 48-h Trials in Moderate to Severe Acute Pain (Trials 1 and 2, Pooled).[1,39] The Most Common Adverse Effect was Pruritus Followed by Muscle Spasm, Increased Blood Creatine Phosphate, and Rash in All Three Treatment Groups. Hydrocodone/Acetaminophen (HB/APAP) Group Had the Highest Incidence of Pruritus, But Suzetrigine Group Showed Increased Incidence of Other Side Effects.

pain signaling pathway.[50] Immunohistochemical analysis revealed the highest immunoreactivity in Aδ fibers, followed by C-type and Aα/β nociceptive fibers. Thus, $Na_V1.8$ is involved in chronic pain.[47,50] Nociceptors express $Na_V1.8$ more than mechanoreceptors.[23,50] $Na_V1.8$ functions by cyclical opening and closing, called the gating mechanism. Among all Na_V subtypes, $Na_V1.8$ requires strong depolarization or a high voltage threshold for activation or opening. For longer, stable Na^+ influx, a prolonged open state gives a sustained action potential or pain signal transmission, that is, $Na_V1.8$ inactivation is slow.[37] Subsequent voltage-gated K^+ efflux restores the resting membrane potential.[11] It is active regardless of Na_V subtypes.[51] This explains its role in the development of neuropathic pain.[52] Rapid recovery from inactivation causes repetitive pain signals.[9] Gain or loss of function mutation in $Na_V1.8$ predisposes chronic pain.[38,48] Thus, $Na_V1.8$ plays a role in both nociception and chronic pain.[9,48]

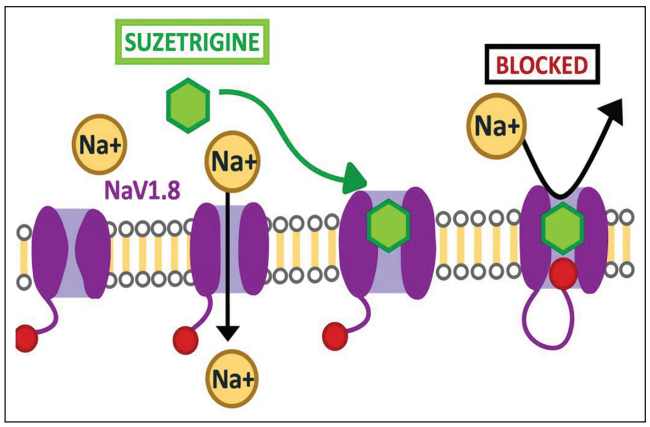


Figure 4. Mechanism of Action of Suzetrigine.[1,39] Suzetrigine Selectively Blocks $Na_V1.8$ Voltage-gated Sodium Channel in the Peripheral Nervous System, Blocking Sodium Ion (Na^+) Influx, Thereby Reducing Transmission of Pain Signal to the Central Nervous System.

Source: Created by the corresponding author using Paint software.

Mechanism of Action

Suzetrigine selectively binds to VSD2, producing $Na_V1.8$ blockade and preventing sodium influx needed for nociceptive signaling between neurons by stabilizing the channel in a closed or inactive state.[37,39] This mechanism is illustrated in Figure 4.

Dosage and Administration

Suzetrigine is available as a 50 mg oral tablet. The recommended loading dose is 100 mg, to be taken in a fasting state, either 1 h before or 2 h after a meal. The maintenance dose of 50 mg is started 12 h after the loading dose, and subsequent doses are repeated every 12 h. The treatment duration is a maximum of 14 days, as studies have not covered beyond this duration of intervention. In patients with moderate hepatic impairment, especially Child–Pugh Class B, the fifth and subsequent doses are given at 24-h intervals. In case of missing a single dose or ≥2 doses, patients were advised to take the missed dose (one tablet for a single missed dose and two tablets for skipping ≥2 doses) and continue the next scheduled dose at the recommended time. For patients with hepatic impairment or under CYP3A inhibitor, on missing a dose, if the next scheduled dose is within or equal to 6 h, the missed dose is to be skipped and the next scheduled dose is to be taken. If the time to take the next dose is more than 6 h, it is advised to take the missed dose and continue with the next scheduled dose.[1,39] In patients with eGFR 15 to <60 mL/min, pharmacokinetic parameters were unaltered. Given that patients with renal impairment or an eGFR less than 15 mL/min were not included in the study, it is advised to avoid using suzetrigine in this population as a precautionary measure.[39]

Table 4: Effect of Suzetrigine on Cytochrome P Enzymes.[1,39]

Cytochrome P450 Enzymes	Inhibited	Induced
Suzetrigine	CYP2C8 CYP2C9 CYP2C19	CYP3A CYP2B6 CYP2C8 CYP2C9 CYP2C19

Clinical Indications

Suzetrigine has been used for the management of moderate to severe acute pain of both surgical and non-surgical etiologies, backed by evidence from clinical trials.[39] As the study period in the trials was up to a maximum of 14 days, the chronic use of the drug and its potential for harm or more benefits are yet to be concluded. Trials have been extended to common chronic pain conditions, such as lumbosacral radiculopathy and diabetic peripheral neuropathy, and the results of these trials will further test the long-term use of suzetrigine. Based on their observations, some studies suggest the use of suzetrigine with other non-steroidal anti-inflammatory drugs (NSAIDs) as a combination therapy for better pain relief.[51]

Drug and Food Interactions

As a CYP3A4 inducer, suzetrigine induces the metabolism of CYP3A4 substrates, such as direct oral anti-coagulants (DOACs). This raises the risk of thromboembolism when both drugs are administered concomitantly, necessitating dose monitoring or avoidance of coadministration.[53] The effects of suzetrigine on cytochrome P enzymes are listed in Table 4.

On administering 100 mg of suzetrigine with high-, moderate-, and low-fat meals, the plasma concentration of the drug and its metabolite M6-SUZ declined, unlike in the fasting state. However, the fed state is predicted not to affect subsequent maintenance doses due to no change in the systemic response. The effect of food on the time to onset of action is shown in Figure 1. Based on the delayed T_{max} and initial plasma concentration with moderate- and high-fat meals, the consumption of the loading dose of 100 mg in the fasting state, that is, 1 h before or 2 h after food. Subsequent doses can be taken with or without food. Consumption of grapefruit-containing foods should be avoided as they inhibit CYP3A4, which metabolizes suzetrigine.[1,20,39] Overall, precautions should be taken, such as avoiding the concomitant use of strong or moderate CYP3A inhibitors, CYP3A substrates, and hormonal contraceptives containing progestin. Additional non-hormonal or alternative contraceptive methods will be needed during treatment and for 28 days after stopping suzetrigine. Precautions related to the dose in patients with hepatic impairment or dysfunction are mandated.[39]

Role in Special Populations

A preclinical study showed placental transfer of suzetrigine in pregnant animal models, but no embryo-fetal effects were observed up to a dose of 100 mg/kg. Furthermore, there was no impact on learning, memory, or sexual maturation in newborns up to 15 mg/kg. As the drug was detected in animal milk, it is also likely to be present in human breast milk. The drug-associated risk of miscarriage, maternal complications, or congenital anomalies is unknown from the trials conducted so far.[39]

The trial participants were primarily middle-aged. The trial included only adults aged >18 years. The pediatric population was not included in any of the studies; without further evidence, the drug is not recommended for this group. The pharmacokinetic parameters among participants aged 18–75 years showed that age had no clinical relevance to suzetrigine.[39]

In patients with hepatic dysfunction or impairment, a low dose is recommended for moderate severity, that is, Child–Pugh Class B. Suzetrigine should be avoided in severe hepatic impairment, that is, Child–Pugh Class C. Suzetrigine should be avoided in patients with eGFR <15 mL/min.[39]

Conclusion

Suzetrigine is a first-in-class $Na_V1.8$ inhibitor approved for the management of moderate-to-severe acute pain. Given its low abuse potential, it is a promising alternative in addressing the global opioid epidemic. Based on clinical trials, this drug is used for the management of moderate to severe acute pain of both surgical and non-surgical etiology. The recommended loading dose is 100 mg, 1 h before or 2 h after food, followed by a maintenance dose of 50 mg, every 12 h. The maximum treatment duration is 14 days. The safety profiles of all clinical trials yielded similar results. Although trials to date have evaluated the efficacy and safety with respect to acute pain, further studies are required to explore its long-term safety and potential as an analgesic for chronic pain. This review suggests the need for further studies on suzetrigine in the pediatric, geriatric, and renal impairment populations.

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Abbreviations

CDC: Centers for Disease Control and Prevention; **CHO:** Chinese hamster ovary; **CNS:** Central nervous system; **CPK:** Creatine phosphokinase; **CYP:** Cytochrome P450; **DOAC:** Direct oral anti-coagulant; DRD2: Dopamine receptor; **DRGS:** Dorsal root ganglionic stimulation; **DSIS:** Daily sleep interference scale; **EA:** Enrichment analysis; **eGFR:** Estimated glomerular filtration rate; **FDA:** Food and Drug Administration; **GRIN2B:** Glutamate receptor; **GWAS:** Genome-wide association study; **HEK:** Human embryonic kidney; **IASP:** International Association for the Study of Pain; **ICD:** International Classification of Diseases; **IC50:** Half-maximal inhibitory concentration; **LC–MS:** Liquid chromatography–mass spectrometry; **LS:** Least square; **NaV:** Voltage-gated sodium channels; **ND7/23:** Rodent neuroblastoma fusion; **NGS:** Next generation sequencing; **NMDA:***N*-Methyl-d-aspartate; **NPRS:** Numeric pain rating scale; **OD:** Once daily; **OPRM1:** μ-Opioid receptor; **OUD:** Opioid use disorder; **PNS:** Peripheral nerve stimulation; **PO:** Per oral; **PPI:** Protein–protein interaction; **SPID48:** Sum of the pain intensity difference over 48 h; **TTX:** Tetrodotoxin; **TTX-R:** Tetrodotoxin-resistant; **TTX-S:** Tetrodotoxin-sensitive; **VSD:** Voltage-sensing domain; **VSD2:** Voltage-sensing domain 2; **WHO:** World Health Organization.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

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ORCID iD

Bala Ashwathy Radhakrishnan Malarvizhi https://orcid.org/0009-0006-3548-3067

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